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Single-Dose Enoxacin Compared with 3-Day Treatment for Urinary Tract Infection

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Oral treatment of simple urinary tract infections generally involves 5 to 7 days of antibiotic therapy. This study with enoxacin, a new antibacterial agent of the quinolone-azaquinolone class, investigated the efficacy of a single dose compared with 3 days of treatment. A total of 154 outpatients with symptoms of simple cystitis were treated in an open randomized study with enoxacin, either one 600-mg dose or 200 mg twice a day for 3 days. A urine sample was collected for culture before treatment, 7 to 10 days after treatment, and 4 to 6 weeks after treatment. Seventy-three patients had positive bacterial cultures from the pretreatment urine sample; the predominant pathogen was *Escherichia coli*, along with a number of other gram-negative organisms and *Staphylococcus* spp. Of these patients, 33 received a single dose of enoxacin and 40 were treated for 3 days. Follow-up examination at 7 to 10 days showed negative urine cultures in 76% of patients from the single-dose group and 89% from the multiple-dose group, a difference that was not statistically significant ($P = 0.665$, Fisher's exact test). A number of patients were lost to follow-up at 4 to 6 weeks. However, of those who did attend, only three patients were shown to have relapsed or become reinfected (two in the multiple-dose group and one in the single-dose group). Enoxacin was well tolerated in both groups of patients; the few adverse events were mostly mild.

Antimicrobial therapy for the treatment of acute, uncomplicated, symptomatic cystitis has been changing over the last 20 years, following a pattern of reducing the duration of therapy. Treatment now commonly consists of 5 to 7 days of therapy, and a number of investigators (4, 6, 9) have reassessed the need to administer antimicrobial agents for even that length of time. The rationale for considering a reduced treatment duration for acute symptomatic cystitis stemmed from the notion that the high levels of antibiotic achieved in urine could be expected to eradicate susceptible pathogens within as little as 24 h. It is also known that patients frequently stop treatment anyway as soon as their symptoms abate, usually after 1 to 2 days.

The advantages conferred by a shortened treatment course, especially a single-dose regimen, are obvious: cost is reduced, side effects are reduced (6), compliance is enhanced, and there is less likelihood of disturbance of normal body bacterial flora, with the associated problems of candidal and opportunistic infection. According to Gleckman (5), another potential value of single-dose therapy is that failure to achieve an immediate bacteriologic response, determined by bacteriuria 2 to 3 days after therapy, serves to indicate that possible tissue invasion and pyelonephritis are present and therefore that more intensive drug therapy, of initially 10 to 14 days, is necessary. However, as a possible disadvantage of short-term therapy, other reports have shown that, rarely, relapsing infection can indeed appear as acute symptomatic pyelonephritis (6, 8), and limited data (10) suggest that this condition, when managed inadequately with single-dose therapy, may fail to respond to subsequent conventional treatment.

Enoxacin is a new antibacterial agent of the quinolone-azaquinolone class that has a broad spectrum of activity against most urinary pathogens (1, 11), including aminoglycoside-resistant strains (3). Enoxacin has been shown to achieve high levels in urine (12; R. R. Bailey and B. A. Peddie, Letter, N.Z. Med. J. **100**:618, 833, 1987) and to be effective in both simple and complicated urinary tract infections with 7 days of therapy (R. R. Bailey and B. A. Peddie, Proc. 14th Int. Congr. Chemother., abstr. no. S-52-3, 1985; M. Huttenen, P. Saloranta, and K. Kunnas, 14th ICC, abstr. no. 5-52-2; K. G. Naber, F. Gutzler, and B. Bartosik-Wich, 14th ICC, S-52-5; R. N. Wyndham, R. Bradbury, and J. R. Bell, 14th ICC, S-52-4). This randomized open study evaluated the advantages and disadvantages of short-term therapy by measuring the safety and efficacy of a single dose of oral enoxacin and of 3 days therapy in the treatment of urinary tract infection.

MATERIALS AND METHODS

Ethical approval was obtained from the local Ethics Committee before the study was begun.

Patient selection and treatment. All patients of either sex, aged between 18 and 70 years and weighing over 45 kg, who presented with symptoms of acute simple cystitis were considered for inclusion in the study. Pregnant or lactating females were excluded from the study (female patients were required to be using adequate contraception, to be postmenopausal, or to be surgically sterilized). Patients with terminal illnesses, hepatic or renal impairment, or quinolone allergy and those requiring concomitant theophylline or other antibiotic therapy were also excluded from the study.

Patients were enrolled sequentially; after fully informed consent was obtained, a sealed envelope was opened to reveal the treatment regimen to which the patient had been randomly assigned: either one 600-mg dose of enoxacin or 3 days of therapy with 200 mg of enoxacin twice daily. The patients were requested to take all of the medication supplied to them, and containers were returned to check for compliance. The diagnosis of cystitis was confirmed by

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culture and colony count of a midstream urine specimen, although therapy was instituted before the culture results were received. Prior unsuccessful antimicrobial therapy did not exclude a patient if a positive base-line urine culture was obtained.

Patient examinations. The base-line urine sample for culture, full patient history, and clinical examination were collected in the 24 h before therapy was started. A blood sample for clinical laboratory studies, full hematological and biochemical screens, was also taken at this time to screen for any abnormalities and again at follow-up to assess any effects of enoxacin therapy.

The clinical examination included measurement of body temperature and assessment of severity of urinary frequency, dysuria, suprapubic pain, low back pain, costovertebral angle tenderness, and macroscopic hematuria (using Ames labsticks).

All patients received a complete follow-up assessment at 7 to 10 days after therapy; this included collection of a urine sample for culture, sampling of blood for clinical laboratory studies, and a clinical examination. Patients who had failed therapy or became reinfected at this time were withdrawn from the study and treated as appropriate. Only those bacteriologically evaluable patients who had a positive urine culture at base line (i.e., $>10^5$ CFU of bacteria per ml) and who had a negative urine culture at this visit were asked to attend for a further follow-up 4 to 6 weeks later. Data on adverse events were also collected throughout the study.

Microbiological studies. Urine was cultured on CLED (cysteine, lactose, electrolyte deficient) medium at 37°C overnight. Isolates were identified as to genus and species and tested by disk diffusion for susceptibility to enoxacin, using a 10-μg disk.

Efficacy assessments. Microbiological efficacy was assessed by urine culture at 7 to 10 days according to the following criteria: cure, $<10^4$ CFU of base-line pathogen per ml; replaced, base-line pathogen replaced by new pathogen; and fail, $>10^4$ CFU of base-line pathogen per ml still present. Patients assessed as microbiological cures at 7 to 10 days were further assessed at 4 to 6 weeks according to the following criteria: cure, base-line pathogen still eradicated; cure with reinfection, infection with a new pathogen; and cure with relapse, base-line pathogen reisolated. Clinical efficacy was assessed at the 7- to 10-day follow-up visit, using the following criteria: cure, complete disappearance of all base-line signs and symptoms; improvement, satisfactory improvement but not complete resolution of signs and symptoms; and fail, no resolution of base-line signs and symptoms. All results were analyzed statistically, using Fisher's exact test (two-tailed), and results were considered significant when P was less than or equal to 0.05.

RESULTS

Of the total of 154 patients who entered the study, 73 had positive pretreatment urine cultures ($\geq 10^5$ CFU of bacteria per ml); 33 of these patients received a single 600-mg dose of enoxacin, and 40 received 200 mg of enoxacin twice daily for 3 days. Four patients, all from the multiple-dose group, are not included in the efficacy analyses; one did not take the medication, two were inadvertently included in the study (they were >70 years of age), and one had an indwelling urinary catheter.

Patient details. Table 1 shows the sex, age, and positive pretreatment urine culture details for the two treatment groups. There were 10 males in the single-dose group but only 3 in the multiple-dose group. However, only two in the single-dose group and one in the multiple-dose group were shown to have positive pretreatment cultures. There was no difference in mean age between the two groups. Urinary frequency was noted in 98% of all patients and 87% of those with positive microbiological findings. Dysuria was evident in 94% of all patients and 97% of those with positive microbiological findings.

TABLE 1. Patient groups[a]

Group	No. of patients and sex	Age (yr) ± SD	No. in group	No. with positive base-line urine culture
Single dose	10 M, 69 F	41.9 ± 17	79	33 (2 M, 31 F)
Multiple dose	3 M, 72 F	43.8 ± 17	75	36 (1 M, 35 F)

[a] M, Male; F, female.

Except for four patients who were thought to have pyelonephritis, all those who entered the study were diagnosed as suffering from cystitis. No testing was available to confirm pyelonephritis; however, two of the four patients had no growth from the base-line urine cultures, and all four were cured both clinically and microbiologically.

Microbiological efficacy. Table 2 shows the urine culture results of the single- and multiple-dose groups (base-line pathogens and enoxacin susceptibilities). *Escherichia coli* was the predominant pathogen in both groups, and all isolates with the exception of two strains of *Staphylococcus saprophyticus* and one strain of *Enterococcus* sp. were susceptible to enoxacin. A small number of patients had a heavy mixed growth of bacteria in the base-line urine cultures; since they also had clinical symptoms, they are included in the analysis.

Table 3 shows microbiological efficacy at the 7- to 10-day follow-up assessment. In the single-dose group, 25 of 33 patients (76%) were bacteriologically cured and 5 of 33 (15%) had replaced infections, for an overall base-line pathogen eradication rate of 91%. One of the three failures was a male patient, another was a 67-year-old female (both were clinically cured), and another was a patient infected with *S.*

TABLE 2. Microbiological of base-line urine cultures

Base-line pathogen(s)	No. of cultures with indicated enoxacin susceptibility test result[a] in group:			
	Single dose		Multiple dose	
	S	R	S	R
Escherichia coli	15	0	21	0
Staphylococcus saprophyticus[b]	4	1	0	1
Coliforms	4	0	7	0
Citrobacter sp.	1	0		
Enterococcus sp.			0	1
Klebsiella sp.	1	0		
Proteus sp.	1	0		
Proteus mirabilis	1	0		
Proteus sp. + *Streptococcus* sp.[c]				
Staphylococcus sp. (coagulase negative)			1	0
Mixed growth[d]				

[a] S, Susceptible; R, resistant.
[b] One isolated in the single-dose group and two in the multiple-dose group were not tested.
[c] One isolate in the single-dose group was not tested.
[d] Three isolates in each group were not tested.

TABLE 3. Microbiological efficacy

Group	No. (%) with given assessment at:						
	7–10 days			4–6 wk[a]			
	Cure	Replaced infection (base line/new pathogen)	Failure	Cure	Replaced or reinfection	Failure or lapse	Lost to follow-up
Single dose (n = 33)	25 (76)	5 (15) (*E. coli*/*E. coli*, mixed growth/*E. coli*, mixed growth/*S. saprophyticus*, 2 *S. saprophyticus*/*S. saprophyticus*)	3 (9) (2 *E. coli*, 1 *S. saprophyticus*)	18	5	4[b]	6
Multiple dose (n = 36)	32 (89)	2 (6) (*E. coli*/*P. aeruginosa*, *E. coli*/*C. freundii*)	2 (6) (1 *E. coli*, 1 mixed growth)	27	3[c]	3[b]	3

[a] Cumulative results.
[b] One patient in each group relapsed at 4 to 6 weeks; both had *E. coli* infections.
[c] One reinfection at 4 to 6 weeks. Base-line pathogen was *S. saprophyticus*; new pathogen was *Klebsiella pneumoniae*.

saprophyticus. In the multiple-dose group at 7 to 10 days, 32 of 36 patients (89%) were cured and 2 of 36 (6%) had replaced infections, for an overall eradication rate of 95%. One of the two failures in this group was a 68-year-old female and the other was a 69-year-old female (who was clinically cured). There was no statistical difference for cure rates between the two groups at 7 to 10 days (P = 0.665).

Nine patients who were cured at 7 to 10 days failed to attend the 4- to 6-week follow-up visit (six in the single-dose group and three in the multiple-dose group). Table 3 also gives the cumulative results obtained at 4 to 6 weeks; the single-dose group contained 18 (19 attended visit) patients with continuation of cures, i.e., urine culture still negative; 27 (29 attended visit) patients in the multiple-dose group had continuation of cure. One patient from the single-dose group who relapsed at 4 to 6 weeks was a 66-year-old female; the other patient who relapsed at 4 to 6 weeks, from the multiple-dose group, was male. The difference between the results from the two groups was not significant (P = 1.00).

Only three male patients entered the study. Two were in the single-dose group; one was a failure and one was lost to follow-up at 4 to 6 weeks because he was thought to have relapsed and received other antibiotic therapy. The single male patient in the multiple-dose group also relapsed at 4 to 6 weeks after therapy.

Clinical efficacy. Clinical efficacy was assessed at 7 to 10 days after therapy for the two groups in those patients with positive base-line urine cultures. In the single-dose group, 30 patients (91%) were cured or improved and three patients, all associated with *S. saprophyticus* infections, failed clinically. One had a heavy mixed growth at base line and developed staphylococcal pyelonephritis at 7 days posttherapy; the other two were bacteriological failures. In the multiple-dose group, 35 patients (97%) were clinically cured. One patient failed; this was also a patient who had an *S. saprophyticus* base-line pathogen, even though the pathogen was eradicated from both follow-up urine cultures. The total cure or improvement rates for the single-dose group, 30 of 33 (91%), and the multiple-dose group, 35 of 36 (97%), were statistically comparable (P = 0.343).

Adverse events. All patients who received enoxacin were assessed for adverse events occurring during the study period. Of the 154 patients, 20 (10 in each group) reported 31 adverse events during the study. These were mostly mild or moderate; none were clinically significant, and no medication was stopped because of adverse events. Four events, all mild or moderate, were considered definitely related to therapy. Table 4 lists the events from the two groups by body system. No difference in the frequency of adverse events between the two groups was found. No clinically significant changes in clinical laboratory values were noted.

DISCUSSION

No statistical difference was shown between the single- and multiple-dose groups at 7 to 10 days for bacteriological cure (76 and 89%, respectively) or the bacteriological eradication (total patients cured or reinfected) rates (91 and 95%, respectively). There was also no statistical difference between the clinical cure rates (91 and 97%, respectively) at 7 to 10 days. At 4 to 6 weeks, the continuation of bacteriological cure in those patients that attended for follow-up also did not differ between the two groups. These results are comparable with those obtained by Greenberg et al. (7), who performed a randomized study of single-dose, 3-day, and 7-day treatment of cystitis in women. In their study, cotrimoxazole given as a single dose and over 3 days gave bacteriological eradication rates of 88% (21 of 24 patients) and 96% (23 of 24 patients), respectively. However, their study also showed an unacceptable failure rate of 53% (9 of 17 patients) with cefadroxil used as a single 1-g oral dose, which indicates that not all antimicrobial agents which are successful with a conventional 5- to 7-day regimen are suitable for single-dose therapy.

Although the numbers are small, the results obtained in this study suggest that 3-day therapy is preferable in cases of

TABLE 4. All reported adverse events in 154 patients by body system, regardless of relationship to therapy

Group	No. of adverse events in given body system							
	Body as a whole (e.g., headache, tiredness)	Nervous system (e.g., dizziness, insomnia)	Digestive system (e.g., nausea, vomiting)	Psychobiologic (e.g., depression, agitation)	Musculoskeletal (myalgia)	Urogenital (early period)	Respiratory system (breathlessness)	Skin (rash)
Single dose (n = 79)	6	6	2	0	1	0	0	1
Multiple dose (n = 75)	4	1	5	3	0	1	1	0

S. saprophyticus infection. Some strains demonstrated enoxacin resistance, and there were one failure and three replaced infections associated with this organism in the single-dose group, whereas 3 days of therapy eradicated the organism in all three cases in the multiple-dose group.

Cystitis in male patients is known to behave differently from that in females, often being complicated by prostatitis or urethritis. Therefore, the small numbers here are inconclusive and suggest that further studies should be performed in men.

The clinical success rate was very high, with an overall mean of 94% for all patients. Interestingly, all four clinical failures were in patients who had *S. saprophyticus* infections, even though the organism was eradicated in one case. A previous study of single-dose enoxacin compared with single-dose amoxycillin (2) also gave high cure rates for simple cystitis, and the results also showed a statistically significantly higher clinical and bacteriological cure rate for enoxacin than for amoxycillin.

The frequency of adverse events reported in this study did not differ between the two groups, and they were mostly mild or moderate; only four were considered to be definitely related to therapy. There appeared to be a higher incidence of neurological adverse events in the single-dose group, possibly because of transient higher blood levels, whereas digestive system upsets were more frequently reported in the multiple-dose group. There were no reported cases of candidal or opportunistic infections, often associated with longer treatment courses of urinary anti-infective agents.

Enoxacin in either single-dose or 3-day treatment appears to be an effective agent for shorter-term therapy of urinary tract infections, particularly in women, with a low incidence of significant side effects.

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